Horizon Scanning in Oncology

Axitinib (AG 013736, Inlyta®) for the second-line treatment of metastatic renal cell carcinoma (mRCC)

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 021
ISSN online 2076-5940

Horizon Scanning in Oncology

Axitinib (AG 013736, Inlyta®) for the second-line treatment of metastatic renal cell carcinoma (mRCC)

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, January 2012

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft in collaboration with The Italian Horizon Scanning Project, Dipartimento Farmaceutico, Azienda ULSS 20, Verona/Italy

Author(s):	Dr. Chiara Poggiani; Italian Horizon Scanning Project, Dipartimento Farmaceutico, Azienda ULSS 20, Verona/Italy
	Katharina Hintringer, BA; LBI-HTA, Vienna
Internal review:	Dr. Anna Nachtnebel, MSc; LBI-HTA, Vienna
External review:	OA Dr. Franz Stoiber; Abteilung für Urologie und Andrologie, Landeskrankenhaus Vöcklabruck

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

This product of collaboration with the Italian Horizon Scanning Project is an offspring of the European network for Health Technology Assessment (EUnetHTA) Project that was supported by a grant from the European Commission. The sole responsibility lies with the author(s), and the Commission is not responsible for any use that may be made of the information contained therein.

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 021
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/dsd.html

1 Drug description

Generic/Brand name/ATC code:

Axitinib (Inlyta®)

Axitinib, AG 013736 / Inlyta / no ATC code yet assigned

Developer/Company:

Pfizer

Description:

Axitinib, a TKI targeting VEGFR

Axitinib is a tyrosine kinase inhibitor (TKI) designed to inhibit the tyrosine kinase activities of the vascular endothelial growth factor receptor (VEGFR) [1]. The VEGFR pathway plays an important role in the pathogenesis and progression of several tumour types and also in renal cell carcinoma (RCC). Signalling via VEGFR is involved in three key tumour processes namely, tumour growth, vascular angiogenesis and metastatic spread [1]. Additional to the VEGFR inhibition, axitinib also binds to and has low potency in platelet-derived growth factor receptor (PDGFR)-β and stem cell factor receptor (c-kit) [2].

recommended daily dose: 5mg twice daily

The recommended daily dose of axitinib is 5mg twice daily administered orally [1]. In phase II and III clinical trials dosing of axitinib was either increased or decreased (dose titration) based on the axitinib-related toxicity profile. If the treatment is well tolerated and no adverse events higher than Grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred for at least 2 weeks, the axitinib dose was stepwise increased from 5mg twice daily to 7mg twice daily and subsequently to a maximum of 10mg twice daily. In case of severe adverse events the axitinib dose was first reduced to 3mg twice daily and then to 2mg twice daily [3-5].

dose titration if tolerated/needed

2 Indication

Axitinib for the second-line treatment of patients with advanced renal cell carcinoma (RCC).

2nd-line treatment in mRCC

3 Current regulatory status

Axitinib is not yet approved as an anticancer drug in Europe or the United States.

not yet approved in Europe or USA

On February 23, 2011, the European Medicines Agency (EMA) granted orphan drug designation for axitinib for the treatment of RCC [6].

orphan drug for mRCC in Europe

FDA seeks advice from the Oncologic Drugs Advisory Committee regarding PFS-benefit and benefit-risk profile

The US Food and Drug Administration (FDA) granted orphan drug designation for axitinib for the treatment of pancreatic cancer, for the treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer, in May 2007 [7]. In April 2011, Pfizer submitted a new drug application (NDA) for axitinib to the FDA. In December 2011 the FDA was seeking advice from the Oncologic Drugs Advisory Committee regarding questions, whether the benefit in progression-free survival (PFS) of the pivotal AXIS trial [3] was generated by a subgroup of patients (cytokine pre-treated) and whether the benefit-risk profile is favourable for axitinib treated patients after failure of first-line systemic therapy in advanced RCC [8].

4 Burden of disease

RCC ~90% of all kidney cancers

RCC is a type of kidney cancer that accounts for approximately 90% of all kidney cancers [9] and 2-3% of all adult malignant tumours [10]. RCC is generally divided into histological sub-types relevant for treatment choice and tumour management: 60-80% are clear cell, 10-15% papillary, 5-10% chromophobe and 5% rare subtypes (e.g. oncocytoma, Bellini duct (collecting duct), etc.) [11].

risk factors: tobacco smoke, obesity and different chemicals

median age at diagnosis: ~60 years

Risk factors for developing RCC are tobacco smoke, which accounts for at least 39% of all cases in males, obesity, exposure to carcinogenic arsenic compounds and several other environmental chemicals [12]. Median age at time of diagnosis of RCC is 60 years and men are more often affected than women (2:1) [10].

~25% of RCC patients (pts) initially diagnosed with metastatic disease

More than 60% of RCC are diagnosed incidentally and only 6-10% show the classic triad of the symptoms haematuria, pain and flank mass [12-13]. Most patients present with systemic symptoms such as weight loss, abdominal pain, anorexia and fever and are diagnosed incidentally by using imaging to investigate a variety of non-specific symptoms [10, 12-13]. About 25% of patients have metastatic disease at time of diagnosis [9] and 20-30% of patients initially diagnosed with localized tumour relapse one or two years after surgery. Of those relapsing after surgery, about 50-60% will develop distant metastasis eventually [14].

TNM staging system – prognostic relevance and influences treatment choice

5-year survival rate: 23-64%

The TNM (Tumour Node Metastasis) staging system is used for clinical staging of RCC, taking the size of tumour, involved lymph nodes and metastasis into account [14]. The TNM staging system is on the one hand a prognostic factor and plays on the other hand an important role in the selection of therapy [13]. In contrast to localized tumours with a high probability of cure (stage I/II), more advanced forms with either metastases in the regional lymph nodes (stage III) or with distant metastases (stage IV) of kidney cancer are linked to poor outcomes. Estimated average 5-year survival rate for patients ranges from 23% (stage IV) to 64% (stage III) [14].

MSKCC risk factors predict short time survival

Risk stratification is important for choosing the most appropriate therapy. The most common model to predict short term survival is the Memorial Sloan-Kettering Cancer Centre or Motzer criteria (MSKCC) which are based on the absence or presence of five risk-factors or predictors, such as serum LDH greater than 1.5 times the upper limit of normal (ULN), haemoglobin level below normal, corrected serum calcium level above the ULN, time from diagnosis and nephrectomy to therapy of less than 1 year and low performance status (Karnofsky performance status (KPS) <70%). Depending on the number of risk factors three groups can be stratified: a good, intermediate or poor risk-group [14]. As the MSKCC criteria are developed and validated based on data derived from patients treated with immunotherapy it is currently unclear, whether and to what extend these prognostic factors are also relevant for patients treated with VEGF-targeted therapy. Thus, Heng et al. conducted a retrospective study to validate the existing MSKCC criteria and other prognostic factors aiming to create a simple clinical-prediction model [15]. This model includes two clinical parameters (KPS <80% and time from diagnosis to treatment <1 year) and four laboratory parameters (hemoglobin <lower limit of normal (LLN), calcium >ULN, neutrophil count >ULN and platelet count >ULN) [15].

3 MSKCC risk groups: good, intermediate, poor

300 newly diagnosed mRCC pts in Austria per year

In 2009, 1,199 patients were newly diagnosed with kidney cancer in Austria. Men were more often affected than women with 707 cases and 492, respectively [16]. Applying the above mentioned estimates, about 300 patients are newly diagnosed with mRCC in Austria per year.

5 Current treatment

6 new targeted agents available

immunotherapy had limited efficacy

targeted agents: TKIs, mTOR inhibitors and monoclonal antibody

Prior to the approval of six targeted agents within the past few years, conventional immunotherapy with interferon (IFN) or interleukin-2 (IL-2) was the standard of therapy in mRCC [17]. While immunotherapy was active in many other cancers it had limited clinical benefit (with response rates between 10-20% [11]) in mRCC and caused considerable toxicities [18]. Since 2006 six targeted agents with different mechanisms of action – TKIs (sunitinib, sorafenib and pazopanib), inhibitors or the mammalian target of rapamycin (mTOR; everolimus, temsirolimus) and a monoclonal antibody (moAb; bevacizumab) – have been approved for the treatment of mRCC.

TKIs (brand name), year of EMA approval:

- Sunitinib (Sutent®), 2006
- Sorafenib (Nexavar®), 2006
- Pazopanib (Votrient®), 2010

mTOR inhibitors (brand name), year of EMA approval:

- Temsirolimus (Torisel®), 2007
- Everolimus (Afinitor®), 2009

Monoclonal antibody (brand name), year of EMA approval:

- Bevacizumab (Avastin®), 2007

Within the clinical trials that led to approval of these agents, all drugs were either compared to IFN and/or placebo but not to another targeted agent. All of these new targeted agents bind to the VEGF receptor [19]. The study population of these pivotal trials was either cytokine-refractory or treatment-naïve except for everolimus, which was compared to placebo in patients who were mainly sunitinib and/or sorafenib refractory [17].

NCCN category 1 recommendation for 2nd-line treatment: everolimus, sorafenib, sunitinib and pazopanib

According to the treatment guidelines by the National Comprehensive Cancer Network the following agents have a category 1 recommendation for second-line therapy in stage IV mRCC with predominantly clear cell histology:

- everolimus,
- sorafenib,
- sunitinib
- and pazopanib.

The three TKIs are recommended as second-line agents after failure of cytokine-based therapy and everolimus, currently the only targeted agent explicitly approved and studied as second-line agent [17], is recommended after failure of a TKI as first-line agent [10, 14].

Currently, one of the main concerns in mRCC is to conduct head-to-head comparisons of the approved targeted agents and to find the optimal sequence of therapy for patients with certain characteristics.

Besides axitinib, further agents like tivozanib and dovotinib are in clinical development [2].

6 Evidence

literature search in 4 databases

In addition to a free text search including the websites of the EMA and of the US FDA, a literature search was conducted in Medline, EMBASE, DARE (Database of the Centre for Review Dissemination of the National Institute of Health) and Cochrane Central on November 15, 2011 by the LBI-HTA.

Only randomized clinical trials which tested axitinib in the indication of interest (i.e. second-line therapy in patients with advanced RCC) were included in the evaluation of efficacy. For the evaluation of safety also uncontrolled trials which tested axitinib in the indication of interest regardless of the investigated outcomes were considered.

one phase III trial included

Overall, one phase III trial, the AXIS trial [3], met the selection criteria for efficacy evaluation. For safety evaluation two further single-arm phase II trials [4-5] were included. No additional trials to those presented in the Horizon Scanning report of the Italian Horizon Scanning Project (IHSP) [20] were identified.

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 Trial (Rini et al. 2011 [3])			
Study identifier	Study No: AXIS Trial, ClinicalTrials Identifier: NCT00678392; Sponsor Protocol Number: A4061032 EudraCT Number: 2008-001451-21		
Design	Phase III, randomised, open-label, multicentre (175 sites in 22 countries (USA, Poland, Russia, UK, France, Taiwan, Spain)), active-controlled trial		
	Duration	Enrolment: Sept 2009 – July 2010 Median follow-up: study still ongoing, (completion planned in 2015) Cut-off date for analysis: Aug 31, 2010 Final OS analysis: November 1, 2011 [21]	
Hypothesis	Superiority – study is powered 90% on a one-sided log-rank test at a significance level of 0.025 to show an improvement in PFS from 5 months with sorafenib to 7 months with axitinib		
Funding	Pfizer Inc; involved in the design of the study, collection and analysis of the data		
Treatment groups	Intervention (I)	axitinib at a starting dose of 5 mg twice daily for ≥2 weeks. Then dose escalation to 7 mg twice daily and then to 10 mg twice daily. Higher doses should be used unless blood pressure was >150/90 mmHg or patient was receiving anti-hypertensive medication. Axitinib doses could be reduced to 3 mg twice daily and then to 2 mg twice daily, if needed.	
	Control (C)	starting dose of 400 mg twice daily. Dose could be reduced to 400 mg once daily and then to 400 mg every other day, if needed because of toxic effects	
Endpoints and definitions	Progression free survival (primary endpoint)	PFS	time from randomisation to either first documented RECIST v1.0. -progression or all-cause death; assessed by an independent, blinded radiology review committee
	Overall survival (secondary endpoint)	OS	time from randomisation to death from any cause
	Objective response rate (secondary endpoint)	ORR	according to RECIST v1.0. (Response Evaluation Criteria in Solid Tumours)
	Duration of Response (secondary endpoint)	DoR	time from randomisation to RECIST v1.0. documentation
	Time to deterioration	TTD	a composite endpoint defined as time between randomisation to first occurrence of death, disease progression, or worsening of symptoms either measured by a) FKSI-15 and b) FKSI-DRS
	Functional Assessment of Cancer Therapy **K**idney **S**ymptom **I**ndex questionnaire	FKSI	assessments took place at baseline and at day 1 of every 4-week cycle; symptom deterioration was defined as two consecutive available decreases of at least 5 points from baseline unless it was the final score, for which one decrease was sufficient

	FKSI–Disease-Related Symptoms	FKSI-DRS	assessments took place at baseline and at day 1 of every 4-week cycle; symptom deterioration was defined as two consecutive available decreases of at least 3 points from baseline unless it was the final score, for which one decrease was sufficient
Results and analysis			
Analysis description	Efficacy population (n): 723 (ITT analysis) (Axitinib: 361 vs. Sorafenib: 362) Safety population (n): 714		
Analysis population	Characteristics		Sex: Males I 73% vs C 71%, Females I 27% vs C 29% Ethnicity: White: I 77% vs C 74%, Black: I <1% vs C 1%, Asian I 21% vs C 22%, Other I 1% vs C 2% Median age (range): I 61 yrs (20-82 yrs) vs C 61 yrs (22-80 yrs) ECOG-PS 0: I 54% vs C 55%; ECOG-PS 1/>1: I 45% / <1% vs C 44% / 0% MSKCC risk groups (%; favourable/intermediate/poor/NA): I 28/37/33/2 vs C 28/36/33/3 Heng et al. risk factors (%, favourable/ intermediate/ poor/ NA): I 18/65/10/6 vs C 22/62/9/7 Previous systemic therapy with: Sunitinib: I 54% vs C 54% Cytokines: I 35% vs C 35% Bevacizumab: I 8% vs C 8% Temsirolimus: I 3% vs C 3%
	Inclusion criteria		histologically or cytologically confirmed RCC with a clear-cell component; all patients had measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST, version 1.0) and RECIST-defined progressive disease as assessed by investigators after one previous systemic first-line regimen with a sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine-based regimen, which reflected all regimens with regulatory approvals at the time of study design; ≥2 weeks since end of previous systemic treatment (≥4 weeks for bevacizumab + interferon-alfa); ECOG PS: 0 or 1; life expectancy of 12 weeks or more; adequate renal, hepatic and haematological organ function.

	Exclusion criteria	history of malignancy other than RCC; present use or anticipated need for CYP405-3A4-inducing, or CYP1A2-inducing drugs; known HIV or acquired immunodeficiency syndrome-related disease; CNS metastasis; uncontrolled hypertension; myocardial infarction, uncontrolled angina, congestive heart failure, or cerebro-vascular accident within previous 12 months; deep vein thrombosis or pulmonary embolism within previous 6 months.	
Descriptive statistics and estimated variability	Treatment group	*Intervention (axitinib)*	*Control (sorafenib)*
	Number of subjects	361	362
	Median PFS, months 95% CI	6.7 6.3 to 8.6	4.7 4.6 to 5.6
	Median PFS according to previous treatment, months (95% CI)		
	Cytokine (34% of pts)	12.1 (10.1 to 13.9)	6.5 (6.3 to 8.3)
	Sunitinib (54% of pts)	4.8 (4.5 to 6.4)	3.4 (2.8 to 4.7)
	Bevacizumab (8% of pts)	4.2 (2.8 to 6.5)	4.7 (2.8 to 6.7)
	Temsirolimus (3% of pts)	10.1 (1.5 to 10.2)	5.3 (1.5 to 10.1)
	ORR, n (%) 95% CI	70 (19%) 15.4 to 23.9	34 (9%) 6.6 to 12.9
	Best ORR, n (%)		
	CR	0	0
	PR	70 (19)	34 (9)
	SD ≥20 weeks	96 (27)	77 (21)
	SD <20 weeks	84 (23)	120 (33)
	PD	78 (22)	76 (21)
	Indeterminate*	22 (6)	42 (12)
	Median DoR, months 95% CI	11 7.4 to not estimable	10.6 8.8 to 11.5
	Median TTD by FKSI-15, months 95% CI	3.1 2.8 to 4.5	2.8 2.7 to 3.0
	Median TTD by FKSI-DRS, months 95% CI	3.7 2.8 to 4.6	2.9 2.8 to 3.5
	Median OS [21], months 95% CI	20.1 16.7 to 23.4	19.2 17.5 to 22.3

Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	Median PFS	HR	0.665
		95% CI	0.544 to 0.182
		P value	<0.0001
	PFS according to previous treatment	HR (95% CI, p-value)	
		Cytokine	0.464 (0.318 to 0.676, p<0.0001)
		Sunitinib	0.741 (0.573 to 0.958, p = 0.0107)
		Bevacizumab	1.147 (0.568 to 2.317, p = 0.6366)
		Temsirolimus	0.511 (0.140 to 1.865, p= 0.1425)
	ORR	HR	-
		95% CI	-
		P value	0.0001
	Median TTD by FKSI-15	HR	0.829
		95% CI	0.701 to 0.981
		P value	0.014[#]
	Median TTD by FKSI-DRS	HR	0.838
		95% CI	0.707 to 0.993
		P value	0.0203[#]
	Median OS	HR	0.969
		95% CI	0.800 to 1.174
		P value	0.374

**Indeterminate included patients with no post-baseline scans, target lesions that were indeterminate at subsequent timepoints, or patients randomised and not treated; [#]p-values based on one-sided log-rank test*
Abbreviations: ITT analysis – intention to treat analysis; vs – versus; yrs – years; ECOG-PS – Eastern Cooperative Oncology Group performance status; MSKCC – Memorial Sloan-Kettering Cancer Center; NA – not available; CR – complete response; PR – partial response; SD – stable disease; PD - progressive disease; HR – hazard ratio; 95% CI – 95% confidence interval

Table 2: Common treatment-emergent all-causality adverse events (AE) and overall AE overview

Study ID NCT00678392					
Grade (according to CTCAE version 3.0) [22]	**Outcome** Number of patients (%)	**Intervention** (n=359)		**Control** (n= 355)	
		All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
	Diarrhoea	197 (55%)	38 (11%)	189 (53%)	26 (7%)
	Hypertension	145 (40%)	56 (16%)	103 (29%)	39 (11%)
	Fatigue	140 (39%)	41 (11%)	112 (32%)	18 (5%)
	Decreased appetite	123 (34%)	18 (5%)	101 (29%)	13 (4%)
	Nausea	116 (32%)	9 (3%)	77 (22%)	4 (1%)
	Dysphonia	111 (31%)	0	48 (14%)	0
	Palmar-plantar erythrodysaesthesia	98 (27%)	18 (5%)	181 (51%)	57 (16%)
	Weight decreased	89 (25%)	8 (2%)	74 (21%)	5 (1%)
	Vomiting	85 (24%)	12 (3%)	61 (17%)	3 (1%)
	Asthenia	74 (21%)	19 (5%)	50 (14%)	9 (3%)
	Constipation	73 (20%)	4 (1%)	72 (20%)	3 (1%)
	Hypothyroidism	69 (19%)	1 (<1%)	29 (8%)	0
	Cough	55 (15%)	3 (1%)	59 (17%)	2 (1%)
	Mucosal inflammation	55 (15%)	5 (1%)	44 (12%)	2 (1%)
	Arthralgia	54 (15%)	5 (1%)	39 (11%)	5 (1%)
	Stomatitis	54 (15%)	5 (1%)	44 (12%)	1 (<1%)
	Rash	45 (13%)	1 (<1%)	112 (32%)	14 (4%)
	Alopecia	14 (4%)	0	115 (32%)	0
	Haematology Laboratory Abnormalities*				
	Anaemia	113/320 (35%)	1/320 (<1%)	165/316 (52%)	12/316 (4%)
	Haemoglobin elevation	31/320 (10%)	NA	3/316 (1%)	NA
	Neutropenia	19/316 (6%)	2/316 (1%)	26/308 (8%)	2/308 (1%)
	Thrombocytopenia	48/312 (15%)	1/312 (<1%)	44/310 (14%)	0
	Lymphopenia	106/317 (33%)	10/317 (3%)	111/309 (36%)	11/309 (4%)
	Chemistry laboratory abnormalities*				
	Creatinine elevation	185/336 (55%)	0	131/318 (41%)	1/318 (<1%)
	Hypophosphataemia	43/336 (13%)	6/336 (2%)	158/318 (50%)	51/318 (16%)
	Hypercalcaemia	19/336 (6%)	0	5/319 (2%)	0
	Hypocalcaemia	132/336 (39%)	4/336 (1%)	188/319 (59%)	5/319 (2%)
	Lipase elevation	91/338 (27%)	16/338 (5%)	148/319 (46%)	47/319 (15%)

	Overall Safety Overview, n (%) [21]		
	Adverse Events	342 (95)	347 (98)
	Grade 3	181 (50)	182 (51)
	Grade 4	21 (6)	36 (10)
	Discontinuations due to AEs	33 (9)	46 (13)
	Serious AEs	106 (30)	24 (7)
	Deaths	113 (31)	109 (31)
	Deaths during treatment or within 28 days from last dose	36 (10)	24 (7)
	Due to disease progression	26 (7)	17 (5)
	Due to reason other than disease progression	10 (3)	7 (2)
	Treatment-related deaths	4 (1)	5 (1)

**Denominator for each laboratory abnormality differed depending on the availability of baseline and at least one on-study test result.*

723 pts (I 361 vs C 362)

median age: 61 years

>50% of pts were sunitinib pre-treated

The phase III open-label AXIS trial (NCT00678392) [3] was conducted in 723 patients (64% at intermediate risk according to Heng model [15]) with median age of 61 and with mRCC pretreated with sunitinib (54%), cytokine (35%), bevacizumab (8%) or temsirolimus (3%). Patients were randomised to receive oral axitinib (5 to 10 mg twice daily) or oral sorafenib (initial dosage of 400 mg twice daily).

+2 months median PFS in axitinib arm vs. sorafenib

+5.6 median PFS in pts pre-treated with cytokine compared to +1.4 in pts pre-treated with sunitinib

Major efficacy result of the pivotal AXIS trial is the statistically significant increase in median PFS of 2 months in the axitinib treated group compared to the control group (HR 0.665; 95% CI: 0.544 to 0.182; $p<0.0001$). Subgroup analysis of median PFS according to previous treatment shows that the increase in PFS is even higher in patients pre-treated with cytokines (+5.6 months) and temsirolimus (+4.8 months) compared to pre-treatment with the VEGFR targeting agents sunitinib (+1.4 months) or bevacizumab (-0.5 months). Comparing the control and intervention group, the increase in median PFS was statistically significant in cytokine and sunitinib pre-treated patients, not in bevacizumab or temsirolimus, which might be due to the small number of included patients within the subgroups. The objective response rate was higher in the axitinib group (19%) than in the sorafenib group (9%) and the median duration of response differed by 0.4 months between these two groups.

After progression on study treatment patients with progressive disease did not cross over to the other arm, but within the axitinib arm 26.7% (50 of 187) who had progressed remained on axitinib and 28% (n=101) received a post-progression systemic therapy; 34.7% (74 of 214) of patients with progressive disease in the control arm remained on sorafenib and 36.7% (n=133) received a post-progression systemic therapy [8]. The different post-progression treatment regimens make it difficult to measure the effect of axitinib on overall survival (OS) compared to sorafenib as the subsequent active therapy cannot yet be statistically controlled and will influence OS to an extent that is difficult to quantify [18]. In December 2011 Pfizer presented the final OS data to the Oncologic Drugs Advisory Committee, which did not demonstrate superiority of axitinib over sorafenib (HR 0.969, 95% CI 0.800 to 1.174; p=0.376) with a median OS of 20.1 and 19.2 months in the axitinib and sorafenib groups, respectively [18].

no cross-over after progression

post-progression therapies make it difficult to measure the effect of axitinib on OS

no difference in OS between treatment groups

The aspect of quality of life (QoL) was quantified using a composite endpoint consisting of time to death, disease progression, or worsening of symptoms. The latter was measured with the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) and the FKSI Disease-Related Symptoms (FKSI-DRS). Measurement of time to deterioration with both instruments lead to a risk reduction in the axitinib group compared to the sorafenib group of 17% and 16% with the FKSI-15 and FKSI-DRS questionnaire, respectively.

QoL was incorporated in a composite endpoint

Within the AXIS trial, main adverse events (AEs) with axitinib vs. sorafenib were diarrhoea (55% vs. 53%); hypertension (40% vs. 29%); fatigue (39% vs. 32%); nausea (32 vs. 22%); dysphonia (31% vs. 14%); palmar-plantar erythrodysaesthesia (27% vs. 51%); vomiting (24% vs. 17%); asthenia (21% vs. 14%); hypothyroidism (19% vs. 8%); stomatitis (15% vs. 12%). Laboratory abnormalities more frequently found with axitinib than with sorafenib were haemoglobin elevation (10% vs. 1%); hypercalcaemia (6% vs. 2%); creatinine elevation (55% vs. 41%); thrombocytopenia (15% vs. 14%).

AEs were generally more frequent and severe in the intervention group

Discontinuations due to AEs were 22 (6%) and 33 (9%) with axitinib and sorafenib, respectively and discontinuations due to treatment–related AEs were twice as frequent in the sorafenib group than in the axitinib group (I 4% vs C 8%). No treatment-related deaths were observed in the axitinib group but two patients died in the sorafenib group.

discontinuations due to (treatment-related) AEs were more frequent in the control group

6.2 Further studies - safety

Two single-arm, open-label phase II trials assessing the safety and efficacy of axitinib in 114 pre-treated patients were identified (NCT00282048) [4] (NCT00076011) [5]. Objective response rate (ORR according to RECIST criteria) was the primary endpoint in both trials. ORR was 22.6% (95% CI 12.9% to 35.0%) and 44.2% (95% CI 30.5% to 58.7%) within those two trials, respectively.

2 single-arm, open-label phase II trials

primary outcome: ORR

Generally the most frequent reported AEs in single-agent axitinib trials are hypertension, fatigue and gastrointestinal toxicities [1]. In the trial with cytokine-refractory patients, 28 of the 52 individuals (i.e. 54%) experienced treatment-related grade 3-4 AEs, the most common ones being hypertension (15%), diarrhoea (10%) and fatigue (8%) [5]. In sorafenib-pretreated patients the most common grade 3-4 AEs were fatigue, hypertension and hand-

most common AEs on phase II axitinib trials: hypertension, fatigue and gastrointestinal toxicities

foot syndrome (each 16.1%), lymphopenia (16.4%) dyspnoea (12.9%), diarrhoea (14.5%) and abdominal pain (11.3%) [4].

7 Estimated costs

no cost estimates yet available for Austria

No cost estimates for Inlyta® are available yet in Austria.

The estimated monthly treatment costs for the other three approved TKIs range from € 3,300.- to € 5,500.- per month and for everolimus [9, 23-25], currently the only targeted agent approved for second-line therapy, estimated monthly treatment costs are € 3,600.- [26]. It is thus rather likely that the costs for axitinib will also be within this price range.

8 On-going research

1 ongoing phase III trial registered

Regarding the investigated indication one on-going phase III RCTs was identified at www.clinicaltrial.gov [27] and www.clinicaltrialsregister.eu.

Phase III trial

NCT00920816:

The study is designed to demonstrate that axitinib (AG-013736) is superior to sorafenib in delaying tumour progression in patients with metastatic renal cell cancer. The estimated primary completion date is April 2012.

axitinib investigated in several other tumour entities

Additional, several phase II trials investigating axitinib in RCC are registered at ClinicalTrials.gov. Further, several other phase I and II studies are currently conducted and registered at ClinicalTrials.gov in different indications such as hepatocellular carcinoma, non-squamous non-small cell lung cancer, prostate cancer, melanoma or metastatic colorectal cancer.

9 Commentary

axitinib not yet approved

Inlyta® (Axitinib) is not yet approved for anticancer treatment in Europe or the United States. According to the registered clinical trials at www.clinicaltrial.gov the anti-tumour effect of axitinib is investigated in a variety of cancer types in phase I to III clinical trials.

currently under review by the FDA

The FDA currently reviews Pfizer's approval application of axitinib for the second-line treatment of axitinib after failure of first-line systemic therapy based on the efficacy and safety results of the pivotal AXIS trial [3, 8].

AXIS: first head-to-head comparison of VEGFR targeting TKIs in mRCC

The AXIS trial is the first head-to-head comparison of VEGFR targeting TKIs in the treatment of RCC and it is also the first trial that explicitly compares two active VEGFR comparators in the second-line setting [21]. The rationale of the AXIS trial was that due to a more precise selectivity of axitinib for the VEGFR compared to multi-targeted TKIs like sorafenib, sunitinib or pazopanib, axitinib would improve treatment outcomes and toxicity profiles. Due to the fact that these multi-targeted TKIs inhibit a wide range of other tyrosine kinases and other targets besides the VEGFR, several toxicities that are generally unrelated to the VEGF pathway are observed within clinical trials. These toxicities are often termed as "off-target" effects of multi-targeted TKIs [2].

rationale of the AXIS trial – enhanced selectivity of VEGFR leads to increased efficacy and decreased AEs

sorafenib – appropriate comparator?

Although, everolimus, an oral mTOR inhibitor, is currently the only targeted agent explicitly licensed for second-line treatment of advanced RCC, sorafenib was chosen as the active comparator as it was considered to be standard of care at the time of AXIS trial initiation and everolimus was still in clinical development [3, 8]. It has to be noted though, that sorafenib was licensed and studied in mRCC patients when immunotherapy with IFN or IL-2 failed [9], but >50% of the AXIS study population were sunitinib-refractory, a population in which the efficacy of sorafenib has not been investigated in a phase III trial yet.

primary outcome, PFS, significantly improved

The primary outcome of the AXIS trial, median PFS, was statistically significantly increased by 2 months in the axitinib group compared to the sorafenib group. An analysis of median PFS according to the type of pre-treatment patients had received, raises the question whether the PFS benefit is driven by the 35% of patients pre-treated with cytokines (difference in median PFS: 5.6 months; compared to the median PFS increase of 1.4 months in sunitinib pre-treated patients) [8]. ORR was higher in the intervention group (19%) compared to the control group (9%), but no complete responses were observed in any group [8].

effect driven by the subgroup of cytokine pre-treated pts ?

Overall, the frequency and severity of AEs were comparable between axitinib and sorafenib. The most frequent (>10%) grade 3 or 4 AEs were hypertension, diarrhoea and fatigue in the axitinib group and hypertension and palmar-plantar erythrodysaesthesia in the sorafenib group. More patients in the sorafenib group (13%) discontinued treatment due to AEs than in the intervention group (9%), but serious AEs were more frequent in the axitinib group (31%) than in the sorafenib group (7%).

limitations: open-label, dose increase only allowed in intervention arm

Limitations of the AXIS trial are, on the one hand, the open-label design, which has the potential to bias the assessment of toxic effects and QoL and, on the other hand, that dose escalations were allowed in the intervention arm only when treatment was well tolerated as mentioned by the investigators but not in the control arm [3].

PFS accepted as primary outcome by regulatory agencies

As already briefly mentioned above, due to the availability of multiple lines of therapy for the treatment of RCC and due to cross-over within several clinical trials, it is problematic to accurately assess the effect of a specific therapy on survival. Thus, regulatory agencies have accepted PFS as a primary outcome in RCC, despite the absence of universally accepted data confirming that PFS is a valid surrogate for OS [28].

future research in mRCC should focus on establishing optimal sequence of available drugs and appropriate patient selection

To date, no curative therapy exists for advanced RCC [10]. Thus, the aim of treatment is symptom palliation, improvement of QoL and extension of OS. With the availability of different therapeutic options, future research should focus on the specific management of RCC patients in terms of establishing an optimal sequence of the available drugs and adverse event management [18]. *Schmidinger et al.* [18] state that the side-effect profiles and the mechanisms of action of these novel agents are crucial for the development of treatment strategies in order to avoid overlapping toxicities and to enable a more rational approach for patient selection. This approach could spare patients unnecessary side effects.

one approach: combine agents that target different receptors → increase efficacy and/or toxicities ?

One way of improving outcomes of patients with mRCC might be to combine agents that target different receptors [11], even though it is unclear which combination is the most efficacious and safe regimen which simultaneously maintains or improves QoL [11, 18].

To sum up, the AXIS trial reached its goal to significantly improve median PFS with axitinib by 2 months compared to sorafenib; difference in median OS was not significant. Sub-group analyses indicate that the treatment effect of both VEGFR targeting agents, axitinib and sorafenib, was less pronounced in the sub-group of patients that failed prior TKI therapy with sunitinib. Thus, the question remains whether axitinib should be recommended for the treatment in patients pre-treated with a TKI targeting VEGFR and how the effectiveness and AE profiles compares to everolimus, the current standard of care in second-line treatment of mRCC after failure of VEGFR targeting TKIs.

References

1. Escudier, B. and M. Gore, *Axitinib for the management of metastatic renal cell carcinoma.* Drugs in R and D, 2011. **11**(2): p. 113-126.
2. Bhargava, P. and M.O. Robinson, *Development of second-generation VEGFR tyrosine kinase inhibitors: current status.* Current Oncology Reports, 2011. **13**(2): p. 103-11.
3. Rini, B., et al., *Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial.* Lancet, 2011. **378**: p. 1931-39.
4. Rini, B.I., et al., *Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma.* Journal of Clinical Oncology, 2009. **27**(27): p. 4462-8.
5. Rixe, O., et al., *Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study.* Lancet Oncology, 2007. **8**(11): p. 975-84.
6. European Medicines Agency. *Public Summary of Opinion on Orphan Designation. Axitinib for the treatment of renal cell carcinomoa (EU/3/10/844).* 2011 6.1.2012]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2011/03/WC500102687.pdf.
7. US Food and Drug Administration (FDA). *Cumulative List of Orphan Products Designations and Approvals per 11/27/2008.* 2008 6.1.2012]; Available from: http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ListsofOrphanProductDesignationsandApprovals/UCM135132.pdf.
8. US Food and Drug Administration (FDA). *FDA Briefing Document - Oncologic Drugs Advisory Committee Meeting, December 7, 2011. NDA 202324, Axitinib (Inlyta®), Pfizer,Inc.* 2011 6.1.2012]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM282290.pdf.
9. European Medicines Agency. *Nexavar: EPAR - Scientific Discussion.* 2007 13.1.2012]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000690/WC500027707.pdf.
10. Escudier, B., V. Kataja, and On behalf of the ESMO Guidelines Working Group, *Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnoss, treatment and follow-up.* Annals of Oncology, 2010. **21(Supplement 5)**: p. v137-v139.
11. Di Lorenzo, G., R. Autorino, and C.N. Sternberg, *Metastatic renal cell carcinoma: recent advances in the targeted therapy era.* European Urology, 2009. **56**(6): p. 959-71.
12. Eble, J.N., et al. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* 2004 12.1.2012]; Available from: http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/bb7-cover.pdf http://www.iranpath.org/Books/Urinary_MG_WHO.pdf.
13. Ljungberg, B., et al. *Guidelines on Renal Cell Carcinoma.* 2010 13.1.2012]; Available from: http://www.uroweb.org/gls/pdf/09_Renal_Cell_Carcinoma%202010.pdf.

14. National Comprehensive Cancer Network. *Kidney Cancer.* 2012 12.1.2012]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
15. Heng, D.Y., et al., *Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study.* J Clin Oncol, 2009. **27**(34): p. 5794-9.
16. Statistik Austria. *Niere (C64) - Krebsinzidenz/Neuerkrankungen pro Jahr), Österreich ab 1983.* 2011 12.1.2012]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/niere/index.html.
17. Pal, S.K. and R.A. Figlin, *Feature article: Renal cell carcinoma therapy in 2010: Many options with little comparative data.* Clinical Advances in Hematology and Oncology, 2010. **8**(3): p. 191-200.
18. Schmidinger, M. and J. Bellmunt, *Plethora of agents, plethora of targets, plethora of side effects in metastatic renal cell carcinoma.* Cancer Treatment Reviews, 2010. **36**(5): p. 416-24.
19. Boehm, S., et al., *Antiangiogenic drugs in oncology: A focus on drug safety and the elderly - A mini-review.* Gerontology, 2010. **56**(3): p. 303-309.
20. Italian Horizon Scanning Project, *AXITINIB for second-line treatment of metastatic renal cell carcinoma.* 2011.
21. Rothenberg, M. *INLYTA® (axitinib).* 2011 6.1.2012]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM283657.pdf.
22. Cancer Therapy Evaluation Program, *Common Termonology Criteria for Adverse Events v3.0 (CTCAE).* 2006.
23. Hintringer, K. *Horizon Scanning in Oncology: Pazopanib (Votrient®) for the treatment of locally advanced and/or metastatic renal cell carcinoma.* 2010 1.12.2012]; Available from: http://eprints.hta.lbg.ac.at/902/1/DSD_HSO_Nr.13.pdf.
24. MedEval GmbH. *AMI - Arzneimittelinformation: Arzneisuche & Interaktionen.* 12.1.2012]; Available from: http://www.ami-info.at/.
25. European Medicines Agency. *Sutent (sunitinib). How is Stutent used?* 2011 12.1.2012]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000687/human_med_001069.jsp&mid=WC0b01ac058001d124.
26. Nachtnebel, A. *Horizon Scanning in Oncology: Everolimus (Afinitor®) for advanced/ metastatic kidney cancer.* 2009 12.1.2012]; Available from: http://eprints.hta.lbg.ac.at/857/2/DSD_HSO_Nr.03.pdf.
27. U.S. National Institutes of Health. *ClinicalTrials.gov.* 2011 12.1.2012]; Available from: http://www.clinicaltrial.gov/ct2/results?term=axitinib.
28. Coppin, C., et al., *Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials.* BJU International, 2011. **108**(10): p. 1556-63.